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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/029,479	LAVI, SARA	
	Examiner	Art Unit	
	Joseph Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-51,65 and 66* is/are pending in the application.

4a) Of the above claim(s) *45-48,53-64 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-51,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
18) ☒ Interview Summary (PTO-413) Paper No(s). 13 .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

This application is a 371 national stage filing of PCT/IB96/01021, filed August 30, 1996 which claims benefit to provisional application 60/003,114, filed September 1, 1995.

Election/Restriction

Applicants amendment filed October 16, 2000 has been received and entered. Claims 1-44 have been canceled. Claims 45-67 have been added and are currently pending.

Applicants have elected Group V, claims 1, 2, and 25-29, drawn to a method of treating cancer in patient by administering **a nucleic acid** encoding PP2C **alpha**, without traverse.

Newly submitted claim 45-48, 52-64 and 67 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 45-49 and 53-64 are drawn to phosphatase 2C alpha and beta **protein** and methods of using said protein for the treatment of cancer. Claims 52 and 67 are drawn to a method of treating cancer in patient by administering a nucleic acid encoding PP2C **beta**.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 45-48, 53-64 and 67 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Election was

made **without** traverse in Paper No. 11. The election has been found proper and therefore made FINAL.

Claims 49-51, 65 and 66 are currently under examination. For the purpose of compact prosecution claim 49 will be read with the limitations encompassed by the elected invention and recited in claim 45.

Claim Objections

Claim 49 is objected to because of the following informalities: Claim 49 depends on non-elected claim 45. Claim 49 should be rewritten as an independent claim with all the embodiments recited in claim 45. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-51, 65 and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 49-51 are drawn to a method of introducing a vector into cancerous cells, wherein said vector comprises a control sequence operatively linked to the nucleic acid sequence encoding protein phosphatase 2C alpha (PP2Ca). Administration of the vector is not specifically limited to *in vivo* or *in vitro*, however when read in light of the specification and the limitation recited in claim 45 to determine the type of cancer, the intended administration is for a method of gene therapy for treatment of cancer by expression of PP2Ca. Claims 65 and 66 specifically recite administration for the treatment of cancer in a patient. The specification teaches one example of PP2Ca expression in colorectal cancer samples where quantitative PCR demonstrates that the level of PP2Ca in cancerous cells is decreased relative to normal surrounding tissue samples (Example 5 and summarized in Figure 8). The specification teaches delivery of a vector to a cell in culture, however is silent with respect to specific teachings of means to deliver a vector to a cancerous cell in a patient.

Three points of enablement are at issue; first, the specification suggests that PP2Ca could be useful in the treatment of cancer because of its role in signaling pathways in a cell, however the specification fails to demonstrate any modification of PP2Ca expression associated with cancer. The single example provided demonstrates that there is not a change in PP2Ca expression in colerectal cancer. Secondly, in the absence of a clear relationship of PP2Ca expression and a cancer phenotype, one of skill in the art would not know the proper levels of PP2Ca which would need to be expressed to affect any form of treatment. Further, the specification teaches human and mouse PP2Ca, however at the time of the claimed invention there many other PP2Ca cloned

from other species which are encompassed by the claims and it is unclear if the PP2Ca form other species which are highly divergent in sequence homology will be capable of complimenting the human and mouse forms of PP2Ca taught in the instant specification. Finally, the specification is silent with respect to any specific vector constructs or methodology for delivery of a vector to a patient which can be used for treatment of cancer in gene therapy protocols.

The instant specification proposes that the use of PP2Ca for treatment of cancer, however the specification and the art of record fail to demonstrate any correlation with changes in PP2Ca expression and any type of cancer. The single example provided in the instant specification demonstrates that the level of PP2Ca is unchanged in cancerous tissues samples as compared to surrounding normal tissue samples from patients with colorectal cancer (Figure 8). A search of the art by the Examiner supports Applicants observation. For example, Kitamura *et al.* in analyzing protein phoaphatases 1, 2A and 2C in hepatocarcinogenesis, demonstrate that while other phosphatases increase in expression levels in a Solt-Farber model the level of PP2Ca is unaltered (Figure 3 and summarized in abstract). Further, when Kitamura *et al.* examine and compare normal liver tissue samples and AH13, a rat hepatoma cell line, they also see no change in PP2Ca expression levels (page 69; figure 4). The instant specification and the art of record both demonstrate that the expression of PP2Ca is unaltered in cells with a transformed cancer phenotype *in vitro* and *in vivo*. In the absence of any guidance on types of cancer one could apply and use PP2Ca for the treatment of cancer, one of ordinary skill in the art would not know how to begin to practice the recited method.

Secondly, in the absence of a correlation between PP2Ca expression levels and a specific type of cancer one of ordinary skill in the art would not know how to affect treatment any of form of cancer. Specifically, even if one of ordinary skill in the art would determine the type of cancer as recited in the claim, the specification fails to teach the level of expression of PP2Ca one must achieve for treatment of a specific type of cancer. The instant specification does demonstrate the use of antisense oligonucleotides to PP2Ca can affect the signaling pathway of infected cells in culture, however in general the use of antisense oligonucleotides decreases the level of expression of a gene product. Though while this specific example does not specifically teach treatment of cancer cells with oligonucleotides, it does suggest that decreasing the amount of PP2Ca expression, not expressing PP2Ca is effective in modifying the phenotype of a cell. Further, in light of the specification and the art of record which demonstrates no change in PP2Ca expression, administration of a vector and expression of PP2Ca may exacerbate the transformed phenotype of a cancer cell. Further, at the time of the claimed invention there were several PP2Ca cloned and characterized from species other than the mouse and human. Klump *et al.* teach a membrane-bound PP2Ca from *Paramecium tetraurelia* and a comparison of this polynucleotide sequence and encoded protein with rabbit, Arabidopsis, yeast and Leishmania demonstrates very low homology (page 32779; summarized in figure 5). Though Klump *et al.* teach that the described PP2Ca share similar enzyme activity *in vitro* on synthetic substrates, there is no teaching in the instant specification nor the art of record demonstrating that these PP2Ca taught by Klump *et al.* share the same enzyme activity as the human form of PP2Ca, nor that the

in vitro data of isolated PP2Ca enzymes can be correlated to *in vivo* activity. In particular, it is well know in the art that there is a codon preference that varies among different species, and in light of the divergent forms of PP2Ca taught in the art (plants, bacteria, yeast and mammals) it is not clear that all these forms could be used to express a PP2Ca polypeptide in a patient, or that once expressed they would have the same enzyme activity and be regulated as an endogenous form of PP2Ca.

Finally, with respect to administration of a vector, at the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two subsequently published reviews. Verma *et al.* teach that as of 1997, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30). Further, besides specific targeting of the virus, the treatment of cancer through the expression of a single gene product has not been obtained. Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system.

Applicants have proposed the expression of PP2Ca for the treatment of cancer in a patient, however essentially all of the work required to ultimately develop therapeutic methods has been left for others. So while altered expression of a polynucleotide encoding PP2Ca may be demonstrated to have a role in cancer, the instant specification has not given the necessary teaching to provide a nexus between the proposed methods in the instant application and the art recognized problems associated with gene therapy. As discussed above, there are several art recognized limitations and unpredictability issues regarding gene therapy, that include: vector to be used for gene expression, production of effective concentration of the candidate polypeptide, delivery of the gene to the appropriated target cell, sustained expression and production of the candidate protein *in vivo*, and maintaining an effective level of the enzyme *in vivo*. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The Applicants have not described nor provided examples of how the recited method of gene therapy differs from those presently found in the art, and in great part rely on the methods of gene delivery established by others, Applicants face the same shortcomings faced by others skilled in the art with regards to the specificity of cell targeting and the ability to regulate gene expression.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to practice the full scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-51, 65 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically;

Claim 49 is unclear because it is drawn to a method of administering a protein to cells, however claim 49 'further includes administrating' of a vector. It is unclear whether the administration step of the vector is in addition or a means wherein the administered nucleic acid produces the protein in the cell. Further, claim 45 is unclear in the recitation of 'cells expressing the cancer' since cancer is a disease not something that is expressed by a cell.

Claim 51 is unclear in the recitation of 'protein phosphatase 2C alpha' because claim 50 is already restricted to protein phosphatase 2C alpha in the restriction requirement.

Claim 65 is incomplete because it recites only administration of a vector and does not include a step were treatment is affected.

Claims 50, 51, 65 and 66 are vague and unclear in the recitation of protein phosphatase 2C alpha because the specification teaches the use and characterization of human protein phosphatase 2C alpha but does not specifically teach the amino acid sequence nor polynucleotide sequences for the human protein phosphatase 2C alpha. At the time of the claimed invention there were several protein phosphatase 2C alpha sequences known in the art from other species. For example Klump *et al.* teach protein phosphatase 2C alpha from Paramecium, Leishmania,

Arabidopsis and yeast, and three isoforms protein phosphatase 2C alpha from Paramecium alone. When read in the light of the specification it is unclear if the recitation of protein phosphatase 2C alpha encompasses only the human form or all the forms known in the art at the time of the claimed invention.

Claim 66 is unclear in the recitation of 'protein phosphatase 2C alpha' because claim 65 is already restricted to protein phosphatase 2C alpha in the restriction requirement.

Double Patenting

Applicant is advised that should claim 50 be found allowable, claim 51 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Applicant is advised that should claim 65 be found allowable, claim 66 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 50 and 65 recite protein phosphatase 2C and claims 51 and 66 recite that the protein phosphatase is protein phosphatase 2C alpha, however claim 50 is already restricted to protein phosphatase 2C alpha by the election of Group V, drawn to a method of treating cancer in patient by administering a nucleic acid encoding PP2C alpha in the restriction requirement.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Saada, M. *et al.*, Gene expression of protein phosphatases in rat ascites hepatoma cell lines, Cancer Detect Prev 18(2):115-122 (1994).

Conclusion

No claim is allowed. Claims 49-51, 65 and 66 are free of the art of record because while the polynucleotides encoding a PP2Ca were known and taught in the art previous to the priority date of the instant application, there was no indication in the art to use PP2Ca in the treatment of cancer in a patient. However, these claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Joseph T. Woitach